CLAIMS

We claim :

1. Method of inhibiting in a mammal formation of neutralizing antibodies directed against an heterologous protein comprising the step of co-administering to said mammal, an agent in an amount sufficient to deplete or inhibit at least some antigen presenting cells of said mammal, and said heterologous protein and/or a nucleic acid sequence encoding said heterologous protein, said agent being administered prior or simultaneously to said heterologous protein and/or a nucleic acid sequence, thereby inhibiting the production of neutralizing antibodies against said heterologous protein.

2. Method according to claim 1, wherein said agent is selected among viruses, liposomes, antibodies, parasites, bacteriae, funguses and or fragments thereof, and nucleic acid sequence encoding said heterologous protein.

3. Method according to claim 2, wherein said virus is selected among adenovirus, adenovirus associated virus, retrovirus, pox virus, vaccinia virus, or fragments thereof.

4. Method according to claim 3, wherein said adenovirus is selected among wild type human adenovirus and recombinant adenovirus, or a fragment thereof.

5. Method according to claims 1 to 4, wherein said antigen presenting cells are antigen presenting cells located in liver of said mammal.

6. Method according to claim 2, wherein said agent is administered prior said heterologous protein and/or said nucleic acid sequence encoding said heterologous protein.

7. Method according to claim 2 wherein said agent is administered simultaneously to said heterologous protein and/or said nucleic acid sequence encoding said heterologous protein.

8. Method according to claim 7, wherein said agent and said nucleic acid sequence encoding said heterologous protein are simulatenously co-administered as a recombinant virus, the genome of which comprising at least nucleic acid sequence encoding said heterologous protein.

9. Method according to claim 8, wherein the genome of said recombinant virus comprises at least regulation sequences necessary to direct the expression of said heterologous protein in at least one antigen presenting cell of said mammal.

10. Method according to claim 9, wherein said regulation sequences comprises promoter sequences selected among cytomegalovirus early promoter (CMV IEP),

Rous sarcoma virus long terminal repeat promoter (RSV LTR), myeloproliferative sarcoma virus long terminal repeat (MPSV LTR), simian virus 40 early promoter (SV40 IEP), major late promoter of the adenovirus.

11. Method according to claims 1 to 10, further comprising the step of administering to said mammal additional agent to enhance the depletion and/or the inhibition of at least some antigen presenting cells of said mammal.

12. Method of inhibiting in a mammal formation of neutralizing antibodies directed against an heterologous protein comprising the step of administering to said mammal a recombinant adenovirus, the genome of which comprising at least a nucleic acid sequence encoding said heterologous protein and regulation sequences, in an amount sufficient to deplete or inhibit at least some antigen presenting cells of said mammal, thereby inhibiting the production of neutralizing antibodies against said heterologous protein.

13. Method according to claim 12, further comprising the step of administering to said mammal additional adenovirus or a fragment thereof, the genome of which not expressing said heterologous protein, thereby enhancing the amount of adenoviruses to deplete or inhibit at least some antigen presenting cells of said mammal.

14. Method according to claims 12 to 13, wherein said mammal is a mouse and wherein the amount of adenovirus particules administered to deplete or inhibits at least some antigen presenting cells of said mouse is equal or greater to 4.10^{10} particles, said particles comprising optionally said additional adenovirus.

15. Method according to claim 14, wherein the amount of adenovirus particules administered to deplete or inhibits at least some antigen presenting cells of said mouse is equal or greater to 6.10^{10} particles.

16. Method according to claims 14 and 15, wherein the amount of said recombinant adenovirus able to form plaque, is equal or greater to 4.10^{9} pfu/mouse.

17. Method of producing transgenic mammal expressing an heterologous protein said method comprising the step of inhibiting in said mammal formation of neutralizing antibodies directed against said heterologous protein by the use of the method of claims 1 to 16 thereby allowing a long-lasting expression of said heterologous protein.

18. Method according to claim 17, wherein the mammal is selected among mouse, rat, rabbit, cow, pig, goat, sheep.

19. Method for reducing an anti-heterologous protein immune response in a mammal, including human, subject to

the administration of said heterologous protein and/or nucleic acid sequence encoding said heterologous protein, said method comprising the step of inhibiting in said mammal formation of neutralizing antibodies directed against said heterologous protein by the method of claims 1 to 16.

20. Method according to claim 19, wherein said method is a step of a gene therapy protocol for the treatment of human afflicted with a disease selected among inheritated or acquired genetic diseases, infectious diseases, inflammatory diseases, autoimmune diseases, cancers, and the associated syndromes thereof.

21. Method for the therapy of a mammal, including humans, afflicted with a disease characterized by the altered expression of an endogenous protein, said method comprising the step of administering to said mammal said protein and/or nucleic acid sequence encoding said protein, and simultaneously or previously, the step of inhibiting in said mammal formation of neutralizing antibodies directed against said protein by the method of claims 1 to 16.

22. Method according to claims 20 and 21, further comprising the step of co-administering simultaneously, separately or sequentially, to said mammal at least one immune modulators selected among cyclosporin, cyclophosphamide, FK506, desoxyspergualine, interleukin-4, interleukin-12, interferon-gamma, anti-CD4 monoclonal

antibody, anti-CD8 monoclonal antibody, anti-LFA1 monoclonal antibody, antibody directed against CD40 ligand or CTLA4Ig.

23. Method of modulating in a mammal formation of neutralizing antibodies directed against an heterologous protein, said method comprising the steps of :

(i) Optionally, co-administering to a first mammal, at least one agent and said heterologous protein and/or a nucleic acid sequence encoding said heterologous protein, said agent being administered simultaneously, sequentially or separately with said heterologous protein and/or nucleic acid sequence, and determining at least one amount of said heterologous protein and said agent, sufficient to trigger an immune response against said heterologous protein by said first mammal; optionally, re-performing step (i) until said amount is determined;

(ii) co-administering to a second mammal said heterologous protein and/or a nucleic acid sequence encoding said heterologous protein, in an amount sufficient to trigger an immune response against said heterologous protein, as determined at step (i) and prior or simultaneously, said agent, in an amount greater that the one determined at step (i) and sufficient to trigger an immune response against said agent and sufficient to deplete or inhibit at least some antigen presenting cells of said mammal, and determining for said second mammal

at least one amount of said agent that reduces and/or suppresses the anti-heterologous protein immune response in said mammal; re-performing step (ii) until said amount is determined; and

wherein,

(a) when one administers to a third mammal, said agent in an amount equal or greater than the one determined at step (i) but lesser than the one determined at step (ii), said mammal produces neutralizing antibodies against said heterologous protein and optionnally against said agent; and

(b) when one administers to said mammal said agent in an amount equal or greater than the one determined at step (ii), said mammal produces neutralizing antibodies against said agent but produces no or few neutralizing antibodies against said heterologous protein.

24. Method according to claim 23, wherein an additional agent is further administered to said mammal in step (i) and (ii).

25. Method according to claims 23 and 24, wherein the amount of said agent of step (ii) is at least twice the amount of said agent determined at step (i).

26. Method according to claims 23, 24, 25, wherein said mammal is a mouse and said agent is an adenovirus, and wherein said agent and said nucleic acid sequence encoding said heterologous protein are simulatenously

co-administered as a recombinant adenovirus, the genome of which comprising at least said nucleic acid sequence encoding said heterologous protein and wherein :

- the amount of said recombinant adenovirus particles of step (i) that triggers an immune response towards said heterologous protein in said mouse without depleting or inhibiting at least some antigen presenting cell of said mouse is below 4.10^{10} particles, and/or the amount of said adenovirus particles able to form plaque is below 4.10^{9} pfu/mouse; and
- the amount of said recombinant adenovirus particles of step (ii) that reduces or suppresses the anti-heterologous protein immune response in said mouse is at least equal or greater than 4.10^{10} particles and/or the amount of said adenovirus particles able to form plaque is equal or greater than 4.10^{9} pfu/mouse.

27. Use of a method according to claim 23 of inhibiting in a mammal formation of neutralizing antibodies directed against an heterologous protein, said method comprising the step of co-administering to said mammal, said heterologous protein and/or a nucleic acid sequence encoding said heterologous protein and prior or simultaneously said agent in an amount equal or greater than the one determined at step (ii).

28. Use of a method according to claim 23 of triggering in a mammal formation of neutralizing

antibodies directed against an heterologous protein, said method comprising the step of co-administering simultaneously, separately or sequentially to said mammal said heterologous protein and/or a nucleic acid sequence encoding said heterologous protein, and said agent in an amount and/or concentration equal or greater than the one determined at step (i) but lesser than the one determined at step (ii).

29. Method for the therapy of a mammal affected by a disease wherein at least one endogenous protein is involved in said disease ethiology, said method comprising the step of inhibiting the biological functions of said endogenous protein by enhancing the production of neutralizing antibodies against said protein by use the method according to claim 23.

30. Method according to claim 29, wherein said disease is chosen among auto-immune diseases, inflammatory diseases, cancers, viral infections, bacterial infections, parasites infections, funguses infections.

31. Use of a method according to claim 28 to produce a mammal with a functional inactivation of at least one endogenous protein, said method comprising the step of administering to a mammal in a simultaneous, separate or sequential manner at least one agent and an heterologous protein and/or a nucleic acid sequence encoding for said heterologous protein, said nucleic acid sequence being

expressed in at least one cell of said mammal, wherein said heterologous protein being substantially identical to said endogenous protein wherein the amount of said heterologous protein, optionally of said agent, that is administered to said mammal is the one determined in step (i), thereby the amount of anti-heterologous neutralizing antibodies produced by said mammal being sufficient to alter the biological activity of said heterologous protein and /or of said endogenous protein.

32. Use according to claim 31, wherein said heterologous protein is at least 50% identical to the endogenous protein.

33. Use according to claim 32, wherein said heterologous protein is a protein selected among animal species, including humans, homologous to said endogenous protein of said mammal.

34. Use according to claim 33, wherein said heterologous protein is mutated in order to enhance its immunogenicity.

35. Method of producing an animal with a functional inactivation phenotype by inactivating at least one endogenous protein, said method comprising the step of triggering in said mammal formation of neutralizing antibodies directed against an heterologous protein being substantially identical to said endogenous protein, said method comprising the step of co-

administering to said mammal in a simultaneous, separate or sequential manner, at least one agent and said heterologous protein and/or a nucleic acid sequence encoding for said heterologous protein, said nucleic acid sequence being expressed in at least one cell of said mammal, wherein the amount of said heterologous protein, optionally of said agent, is at least sufficient to trigger an immune response against said heterologous protein and the amount of said agent is not sufficient to deplete or inhibite at least some antigen presenting cells of said mammal.

36. Mammal obtained by the method of claim 35.

37. Mammal of claim 36, wherein said mammal is a mouse, rat, rabbit.

38. Use of a mammal according to claims 36 and 37 to perform biological, physiological, biochemical, molecular studies and analysis of the function of said heterologous and/or homologous protein.

39. Use of a mammal according to claims 36 and 37 to perform drug screening.

40. Use of a mammal according to claims 36 and 37 to isolate spleen cells from said mammal that expresses antibody directed against said heterologous an/or endogenous protein to make hybridoma(s).

41. Use of biological fluid of the mammal according to claims 26 and 27 to prepare serum and/or polyclonal antibodies.

42. Method to produce vaccine for a mammal, against an heterologous protein, said method comprising the step of triggering in said mammal formation of neutralizing antibodies directed against said heterologous protein, by using the method according to claim 23.

43. Method according to claims 1 to 26 and 33, use of a method according to claim 27 to 32, wherein said heterologous protein or a fragment thereof is selected among the proteins that are presented by class I major histocompatibility molecule (CMH I), a class II major histocompatibility molecule (CMH II), or a combination of a class I major histocompatibility molecule and a class II major histocompatibility molecule.

44. Method according to claim 43, wherein said heterologous protein is chosen among secreted proteins, membranes proteins, receptors, intracellular proteins, nuclear proteins.

45. Method according to claim 44, wherein said secreted protein is selected among neuromediators, hormones, interleukines, lymphokines, interferons, chemokines, growth factors.

46. Method according to claims 1 to 26 and 33, wherein the mammal is chosen among mouse, rat, rabbit, hamster, Chinese pig, cow, pig, goat, sheep, horse, primate.

47. Method according to claims 1 to 26 and 33, wherein the administration of said agent and said heterologous protein and/or nucleic acid sequence encoding said heterologous protein is performed via a technique chosen among intravenous injection, intravaginal injection, intrarectal injection, intramuscular injection, intradermic injection,

48. Method according to claim 42, wherein said intravenous injection is selected among retro-orbital sinus injection, tail injection, hepatic injection, femoral or jugular injection.